PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

G.E. EHRLICH (1995) LTD.
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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	20.04.2006

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
29330	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IL2005/000481	05.05.2005	05.05.2004

Applicant
RENOPHARM LTD.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
29330		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IL2005/000481	05.05.2005	05.05.2004

International Patent Classification (IPC) or national classification and IPC

INV. C07D277/24 C07D277/34 C07D277/40 C07D417/04 C07D277/50 C07D417/12 C07D277/46 A61K31/426 A61K31/4439

Applicant

RENOPHARM LTD.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02.03.2006	20.04.2006

Name and mailing address of the international preliminary examining authority:

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IL2005/000481

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-150	as originally filed

Claims, Numbers

1-198	as originally filed

Drawings, Figures

1-33	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1 -8, 9(part)-19(part), 20-26, 27(part)-198(part)

because:

☒ the said international application, or the said claims Nos. 62-74, 140-198 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☒ the claims, or said claims Nos. 1 -8, 9(part)-19(part), 20-26, 27(part)-198(part) are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*.

see separate sheet

☐ no international search report has been established for the said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	9-19, 27-198
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	9-19, 27-198
Industrial applicability (IA)	Yes:	Claims	9-19,27-61,75-139
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1- Present claims relate to an extremely large number of possible compounds and compositions. Support within the meaning of Art. 6 PCT and disclosure within the meaning of Art. 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope in impossible. Consequently, the search has been carried out for those parts of the claims which appears to be supported and disclosed, namely those parts relating to the compounds of claim 9 wherein B and Z are alkyl groups and Y is a NO releasing group as defined on page 40 (lines 24-33).

The preliminary examination will concern only the parts of the claims which have been searched (Rule 66.1 (e) PCT).

2-Claims 62-74 and 140-198 relate to subject matter considered by this Authority to be covered by the provisions of Rule 67.1 (iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject matter of these claims, cf. Article 34(4)(a)(i) PCT.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1- Reference is made to the following documents:

d1: WO 01/49275 A (QUEEN'S UNIVERSITY AT KINGSTON; THATCHER, GREGORY, R., J; BENNETT, BRI) 12 July 2001 (2001-07-12)

d2: WO 03/086282 A (NITROMED, INC; FANG, XINQIN; GARVEY, DAVID, S; GASTON, RICKY, D; LIN,) 23 October 2003 (2003-10-23)

d3: KUMAR S ET AL: "Design, Synthesis, and Evaluation of alpha-Ketoheterocycles as Class C Beta-Lactamase Inhibitors" BIOORGANIC &

MEDICINAL CHEMISTRY, ELSEVIER SCIENCE LTD, GB, vol. 9, 2001, pages 2035-2044, XP002206636 ISSN: 0968-0896

2- Novelty

Thiazole derivatives bearing a NO-releasing group are disclosed in d1 (cf. compounds IIIf of page 25, IVk of page 33, Vr of page 38 and Vy of page 39).

These compounds are excluded from the scope of present claims either because they have been disclaimed or because the group linking the NO-releasing moiety is not an alkylene chain (present group B).

Hence, the requirements of Art. 33.2 are met.

3- Inventive step

3.1- The applicant seems to have set himself the task of providing novel NO-donors which can be useful in the treatment of various conditions such as cardiovascular diseases, inflammation and tumor.

Documents d1 and d2 relate to compounds having the same use of present compounds.

Considering the chemical structures of the compounds disclosed in these documents, it is considered that d1 represents the closest state of the art.

For the purpose of assessing the inventive activity during the international stage, it is accepted that present compounds possess the claimed activity, i.e. that they are NO-donors.

Hence, the technical problem can be seen in the provision of further NO-donors.

In this context it is observed that taking into account of the experimental data disclosed in the application, it appears that there is no basis for formulating a different technical problem.

In various passages of the description it is underlined that one of the objectives of the invention is to provide NO-donors which does not induce tolerance. The tolerance profile of some compounds of the invention is disclosed from pages 144 to 147 of the description and in Figures 15-24. However, from these data the sole conclusion that can be drawn is that some of the claimed compounds have a better tolerance profile that a specific NO-donor of the prior art, namely the GTN. However, the GTN does not represent the most structurally similar compound known from the state of the art.

In order to be relevant for the definition of the technical problem, the comparative studies

should be carried out using the most similar compounds of the prior art which are the compounds IIIf of page 25, IVk of page 33, Vr of page 38 and Vy of page 39 of d1.
Furthermore, it is understood from the description, that the compounds claimed are designed in a way that upon release of NO a residue of vitamin B1 is formed. This objective has allegedly been achieved by the preparation of compounds which comprise an NO-releasing group which is bound to a thiamine-derived thiazole ring (page 30).
However, it seems that only a limited part of the compounds claimed contain this structural feature. The definition of the substituents of formula (I) is so broad (cf. in particular the groups A and X) that for many of the compounds included in this formula it is not clear how a residue of vitamin B1 could be generated after the NO release.
In fact the application does not provide enough evidence in support of the allegation that the compounds claimed generate vitamin B1 upon NO release.

In view of the above it is considered that the application does not support the formulation of a technical problem different from the one defined above, namely the provision of further NO donors.

3.2- The compounds disclosed in d1 are structurally very similar to the compounds of the invention. Compounds IIIf and IVk are excluded from the scope of the claims merely by means of a disclaimer.
From d1 the skilled person would deduce that thiazole derivatives, eventually substituted in position 4 by an alkyl group and bearing in position 5 a NO-releasing moiety attached to the ring through an alkylene chain, are suitable compounds as NO-donors.
The use of NO-releasing agents for the treatment of cardiovascular disorders is suggested by d2.
Hence, the provision of present compounds as NO-releasing agents does not involve any inventive skill.
The processes of claims 75-139 are based upon standard procedures as it can be deduced from the reaction scheme 7 of d3. Furthermore, on page 78 of the description it is acknowledged that the preparation of a thiazole derivative by reaction of a thioamide with a compound containing an active carbonyl is a well-known procedure (cf. reference to the Hantzsch procedure).
A process based upon common reaction could be regarded as inventive only if limited to the preparation of novel and inventive compounds. However, for the reasons explained

above, this is not the case for present claims 75 to 139.
Hence, also the process claims do not involve any inventive activity.